

REMARKS

Claims 24-30, 32, 33 and 35-46 were examined. In response to the present Office Action, Applicants amended Claim 42 and added Claim 47. No new matter has been added. Accordingly, Claims 24-30, 32, 33 and 35-47 are currently pending. Favorable consideration and allowance of all pending claims are respectfully requested.

The Indefiniteness Rejection

Claim 42 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite and unclear for several reasons.

First, the Examiner suggests that it is unclear how a nucleic acid may encode a gene or another nucleic acid capable of inducing angiogenesis. Applicants respectfully submit that nucleic acids can encode other nucleic acids with biological activity. For example, the nucleic acid (e.g., DNA) may encode an anti-sense RNA that induces angiogenesis by controlling expression of a protein involved in the angiogenesis process. However, in the interest of clarity, Applicants have amended Claim 42 to recite that each desired molecule is a protein and added Claim 47 to indicate that when the desired molecule is a nucleic acid, it encodes an anti-sense RNA capable of inducing angiogenesis or inhibiting angiogenesis.

Second, regarding "contractile protein," Applicants believe that this term is clear and the metes and bounds thereof are well known to those of skill in the art. Contractile protein is an art-recognized term that embraces proteins "having or concerned with the power or property of contracting, such as proteins of muscle fibrils" (Webster's Medical Desk Dictionary, 1986, Merriam-Webster, Inc.). Myosins, troponins and actins are well-known examples of contractile

proteins. Hence the term is clear to those of skill in the art and Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

The Enablement Rejection

Claims 41, 42, 44 and 46 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to use the invention.

Applicants gratefully acknowledge the Examiner's recognition that the generic claims (*e.g.*, Claims 24-40) are enabled as well as claims in which the desired molecule is an "angiogenic protein" (*e.g.*, Claim 43). However, Applicants respectfully submit that the remaining subject matter is enabled as claimed.

The present claims are directed to a specific delivery method of introducing a nucleic acid into cardiomyocytes using rAAV at dosages determined to provide stable and efficient transduction of those cells. Other than Claim 46, no claim (whether or not rejected for lack of enablement) provides that any specific effect is achieved. In this regard, Claim 46 only indicates what particular cardiovascular effect is achieved and not the particular level or degree of the effect. Hence no claim indicates that a specific therapeutic effect is obtained.

According to the Examiner, the rejected claims lack enablement because of the unpredictability of gene therapy, which he essentially translates into the specification's failure to actually demonstrate that each and every indicated molecule in those claims "provide therapeutic effect for a particular cardiovascular disease or condition in a patient *in vivo*" (Office Action, sentence bridging pages 4-5). However, this is not the standard against which to assess enablement.

The Examiner's contention is not applicable to the present scope of the claims. The subject matter in the claims at issue in this rejection provide that the rAAV encoding a particular molecule (*e.g.*, a contractile protein, thymidine kinase, p27 and the like) introduce the molecule into cardiomyocytes using the claimed infusion route. No element of the claims requires a therapeutic effect for a particular cardiovascular disease or condition in a patient *in vivo*. Given that markers and angiogenic proteins such as FGF-5 and VEGF, can be introduced by the claimed method, there is no inherent reason, and the Examiner has not provided one, that the other molecules can not also be introduced by the same infusion method to achieve stable and efficient transduction without undue experimentation—which is the standard against which to assess enablement.

Moreover, the Examiner has maintained this position despite Applicants' declaratory evidence of record from a prominent expert in the gene therapy field, Dr. Michael Parmacek, that those of skill in the art are enabled to practice the claimed invention without undue experimentation. In this regard, the Office Action finds the Parmacek Declaration unpersuasive because of the "unpredictability of the art of gene therapy" (Page 7). Not once does the Examiner discuss, rebut or refute any single aspect, comment, opinion or conclusion of Dr. Parmacek—the declaratory evidence is merely ignored on the basis of gene therapy's unpredictability. Not only is this approach improper but, more importantly, the Examiner has not met his burden of rebuttal by merely stating that gene therapy is unpredictable, particularly in light of the proffered evidence to the contrary. Hence the record establishes, without adequate rebuttal, that the specification and the state of the art enabled one of skill in the art to practice the claimed invention in December 1998. Parmacek Declaration, ¶¶ 23-29. More particularly, it is un rebutted that:

- In December 1998, it would have been a matter of routine experimentation to construct a recombinant AAV vector encoding a desired molecule operably linked to a control region for the transduction of cardiomyocytes. The mechanics of selecting vectors, genes, and promoters and combining them into expression constructs were well known at that time. Moreover, cloned DNA encoding proteins and antisense RNA useful for treating cardiovascular conditions was available for incorporation into these expression constructs. Hence, one of skill in the art at the time of the invention could have selected a combination of rAAV vectors, regulatory elements, such as promoters and genes suitable to produce the expression of a desired molecule in cardiomyocytes. Parmacek Declaration, ¶ 23.
- At the time of the invention, effective transduction of various rodent and human cells using rAAV vectors encoding marker and therapeutic genes had been demonstrated. Parmacek Declaration, ¶ 24.
- Genes encoding markers and therapeutic proteins had been expressed in various organs of animals other than rodents using rAAV vectors administered by some of the same routes known for transduction of rodent cells. For example, canine and primate cells expressed therapeutic genes, Factor IX and amino acid decarboxylase (AADC), respectively, following local injection of rAAV vectors. Parmacek Declaration, ¶ 25.
- At the time of the invention, rAAV vectors had been used to express therapeutically-effective amounts of several genes in the liver, brain, vasculature, and lungs of various non-human animals. A phase I trial to determine the therapeutic effectiveness of rAAV-CFTR gene vectors in human subjects had also been initiated. Parmacek Declaration, ¶ 26.
- The specification and the state of the art enabled one of skill in the art to practice the claimed invention in December 1998. Based on such teaching and guidance in Appellants' specification, along with the state of the art described herein with respect to molecular biological techniques and *in vivo* gene transfer, it was merely a matter of routine experimentation to construct a recombinant AAV vector encoding a desired molecule, deliver it to an animal by infusion into a coronary artery or coronary sinus, and thereby transduce cardiomyocytes perfused through the coronary artery or coronary sinus. Parmacek Declaration, ¶ 27.
- Since the filing of the instant specification, others in the field have done nothing more than follow the teaching of the specification and have successfully transduced mouse cardiomyocytes using rAAV vectors encoding the marker gene β -galactosidase under the control of the CMV promoter. Svensson *et al.* (1999), *Circulation* 99:201-205. Parmacek Declaration, ¶ 28.

Further, it is respectfully submitted that the desired molecules as specified in claims 42 and 44 are reasonably correlated to cardiovascular diseases and conditions and have a function

related to the treatment of a cardiac or cardiovascular disease or condition. The instant specification teaches that proteins useful for treating restenosis include thymidine kinase, cytosine deaminase, p21, p27, p53, Rb and NF- κ B. (page 5, lines 25-26, *inter alia*, of the instant specification). The specification further teaches that angiogenic factors and other proteins useful in the claimed method are those proteins that inhibit vascular smooth muscle cell proliferation; treat arteriosclerosis, treat restenosis, stimulate cardiomyocyte activity, are secreted from cardiomyocytes and exert their effects in the heart or other locations in the body so as to treat a cardiovascular condition or disease. (See, e.g., page 5, lines 14-31, *inter alia*, of the specification).

Thus, based on Applicants' teaching and exemplification, one having skill in the relevant art would reasonably expect that nucleic acids, e.g., antisense nucleic acids, and protein-encoding nucleic acids, which are correlated to treating cardiac disease or disorders, would be expressed in the cardiomyocytes following infusion of rAAV vector according to the claimed method. Moreover, the effectiveness of nucleic acid delivery to cardiomyocytes employing rAAV infused by the claimed method is reasonably expected to include those diseases and disorders of cardiovascular or cardiac tissue, which is comprised of cardiomyocytes, as recited in claim 46.

Finally, Applicants have provided numerous uses for their demonstrated method of stable and efficient gene transfer into cardiomyocytes, namely, (1) delivery of marker genes to study gene expression in the heart; (2) delivery of therapeutic genes to treat acquired and inherited cardiac conditions; and (3) delivery of disease causing genes to create organ and animal models useful in developing therapeutic drugs for those specific diseases. Amendment, March 24, 2003, Page 6, first paragraph.

For marker gene expression studies, the marker genes can be coupled to promoters, or promoter fragments, to assess promoter activity based on the level of marker gene expression. With the appropriate promoters controlling expression of a marker gene, Applicants submit that the presently claimed method can be used to evaluate the regulation and expression of genes in the functioning heart, including hearts in particular disease states, and have provided by way of support a publication of Aikawa et al. (2002, *J. Biol. Chem.*, 277:18979-18985) demonstrating the use of rAAV to evaluate the cardiac muscle-specific alpha myosin heavy chain promoter. Applicants have further provided the publication of Kawada et al. (2002, *Proc. Natl. Acad. Sci. USA*, 99:901-906) evidencing the well-established use of providing a marker gene as a control for experiments in which therapeutic genes are provided. Kawada et al. used rAAV encoding lacZ (aka β -galactosidase) as a control for somatic gene therapy for dilated cardiomyopathy (DCM) in the TO-2 hamster strain receiving rAAV encoding δ -sarcoglycan (δ -SG) and demonstrated delivery of a therapeutically-effective amount of a gene product to treat a cardiac condition using Applicants claimed method of intracoronary delivery.

Moreover, those of skill in the art will also recognize that non-marker genes can be delivered and used to study gene expression in the heart in accordance with the claimed methods. For example, Dr. Parmacek also declared that at the time of the claimed invention, those having skill in the art would recognize utilities for the claimed invention, including uses to deliver genes to establish organ models and animal models for human cardiovascular disease. Parmacek Declaration, ¶ 22.

In conclusion and based on the foregoing, the specification together with the state of art at the time, provided one of skill in the art with sufficient guidance to make and use the full

scope of the claimed invention without requiring undue experimentation. Parmacek Declaration, ¶ 29.

Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

The Anticipation Rejection

Claims 24, 32, 33, 40, 43 and 45 stand rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Hammond *et al.*, PCT Publication No. WO 98/50079 (hereinafter "Hammond").

As is well established, an anticipatory reference must recognize each and every element of the claimed invention, and must be enabling. Hammond fails in this regard. In particular, Hammond does not recognize that the dosage of viral vector is body weight dependent. This is an important and claimed aspect of Applicants' invention.

The presently rejected claims recite, *inter alia*, that the rAAV is delivered to an animal in an amount of about 1×10^5 to about 1×10^9 infectious units (IU) AAV per gram body weight of the animal. Hammond states merely that a certain number of viral particles are delivered no matter what type of animal receives the dosage. Such teaching fails to disclose how to recognize a therapeutically effective amount to obtain stable and efficient transduction. Hammond suggests "typical" ranges of viral particles to use as an "effective dose" of vector (page 38, lines 33-34), but leaves "the exact dose to be administered" to be "determined by the attending clinician" (page 38, line 34 to page 39, line 1) and applies this to all animals of all body types and for any type of viral vector. In fact, Hammond only provides data for adenovirus transduction, and no data whatsoever with respect to rAAV or any other viral vector.

Accordingly, Hammond does not anticipate or enable Applicants' claimed dosages for rAAV based on animal body weight.

Absent such anticipation, Applicants deem this rejection overcome and respectfully seek withdrawal thereof.

The Obviousness Rejection

Claims 24-30 and 35-39 have been rejected under 35 U.S.C. §103(a) as allegedly rendered obvious by Hammond.

Hammond is discussed above and Applicants submit that Hammond's failure to recognize that efficient and stable transduction of cardiomyocytes depends on the dosage of rAAV provided per body weight of the animal, establishes that Hammond does not render obvious the presently claimed subject matter.

It was unexpected at the time of the present invention what amount of rAAV vector per gram body weight of the recipient would lead to efficient and stable transduction of the vector into cardiomyocytes and the stable expression of a desired molecule transduced into the cells. Such a result is not obvious from the teaching of Hammond, which merely suggests a broad range of virus particles to use for generic dosing for all animals without regard to their size (body weight).

It is well established that obvious to try is not a proper standard for the determination of obviousness under § 103. Without carrying out Applicants' infusion method using rAAV vector to transduce cardiomyocytes in a unit amount per animal body weight for the times determined by the Applicants, it would not be obvious as to what those amounts or times were.

In fact the literature taught away from Applicants invention in this regard. In particular, Kaplitt *et al.* (1996) *Ann. Thor. Surg.* 62:1669-1676 ("Kaplitt") discloses the transduction of porcine cardiomyocytes using rAAV encoding β -galactosidase by infusing 10^7 rAAV so that the rAAV was provided at a very low dosages per unit body weight, i.e., much less than 10^4 IU rAAV per gram body weight. The transduction efficiency reported was 0.2%, with only a subset of the transduced cells expressing the transgene up to six-months post-infusion. In contrast, the present invention provides for administering the rAAV for selected time periods and in particular amounts proportional to the body weight of the recipient and achieves expression levels of β -galactosidase greater than 50% throughout mouse myocardium (a transduction efficiency sufficient to provide therapeutic dosages). The present invention provides for 10^5 to 10^9 IU rAAV per gram of body weight and is an unexpected improvement over the methodologies described by Kaplitt, where the rAAV was provided at much lower dosages as indicated above.

Accordingly, neither Hammond nor the state of the art suggest the claimed dosages and times necessary to achieve efficient and stable transduction of cardiomyocytes in accordance with the present invention. Applicants thus deem this rejection overcome and seek withdrawal thereof.

Conclusion


In view of the foregoing amendments and remarks, Applicants submit that the present claims are in condition for allowance, which action is earnestly solicited. The Examiner is invited to contact the undersigned by telephone should any issues remain outstanding.

Respectfully submitted,

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